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REMARKS

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited.

A. Related Applications

The Applicants wish to draw the Examiner's attention to the existence of Applicants' related cases directed to nanoparticle-based compositions, methods of making, and methods of use. Many of these cases have received Office actions and a number of these cases have already issued. These cases are listed in Appendix A (attached).

B. Amendments to the specification

The specification was amended to update the priority claim as well as to correct for a typographical error. No new matter has been added to the application as a result of the present amendment.

C. Amendments to the claims

Claims 434, 436-452, 454-464 and 485 were pending in this case. Claim 445 was amended and new claims 487 and 488 were added. Support for the amendments and new claims can be found in the specification, for instance, at page 31, lines 18 and 19 and Figures 45 and 46. Accordingly, no new matter has been added to the application as a result of the present amendment.

D. Information Disclosure Statements

The Applicants note that the Examiner did not return an executed copy of the PTO 1449 forms for the Information disclosure statement and 5th Supp. Information disclosure statement, both hand delivered to the Examiner on January 15, 2004. Based on the undersigned representative's review of the public PAIR system, these two statements, references and PTO 1440 forms were stamped as received by the Patent Office on January 15, 2004. The Applicants request that the Examiner execute the attached copies of the PTO 1449 forms and return a copy of the same to the undersigned representative.

E. Rejection under 35 U.S.C. section 102(b) based on Hainfeld

Claim 434 stands rejected under 35 U.S.C. section 102(b) as being anticipated by Hainfeld (U.S. Patent No. 5,521,289). Specifically, the Examiner alleges that the invention of claim 434 is old because Hainfeld allegedly disclosed organothiol metal cluster compounds. The Applicants respectfully traverse this rejection.

As a threshold matter, the Federal Circuit has stated that for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. Corning Glass Works v. Sumitomo Electric, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 U.S.P.Q 193, 1098 (Fed. Cir. 1983). Contrary to the Examiner's position, Hainfeld does not disclose the presently claimed invention.

Hainfeld relates to small organometallic probes. While Hainfeld does describe organothiol metal clusters that include organothiols, Hainfeld is completely silent with respect to nanoparticle conjugates having a covalently bound polythiol functional group. See claim 434. Accordingly, Hainfeld does not anticipate claim 434. Withdrawal of this section 102(b) rejection against claim 434 based on Hainfeld is in order and is respectfully requested.

F. Rejection under 35 U.S.C. section 102(e) based on Leone

Claim 434 also stands rejected under 35 U.S.C. section 102(e) as being anticipated by Leone et al (U.S. Patent No. 6,369,206) ("Leone"). Specifically, the Examiner alleged that the invention of claim 434 is old because Leone allegedly disclosed metal organothiol particles, cited to col. 11. Applicants respectfully traverse this rejection and submit that Leone does not disclose or suggest the presently claimed invention.

Leone relates to metal organothiol particles. While Leone does describe organothiol metal clusters that include organothiols, Leone is completely silent with respect to nanoparticle conjugates having a covalently bound polythiol functional group. See claim 434. Accordingly, Leone does not anticipate claim 434. Withdrawal of this section 102(b) rejection of claim 434 based on Leone is in order and is respectfully requested.

G. Rejection under 35 U.S.C. sections 102(e)/103

Claims 434, 436-452, 454-464, and 485 stand rejected as anticipated by or, in the alternative, under 35 U.S.C. section 103(a) as obvious over Yguerabide et al. (U.S. Patent No. 6,214,560) ("Yguerabide"). The Examiner's detailed comments can be found on pages 5-7 of the office action. Applicants respectfully traverse.

The Federal Circuit reiterated the manner in which obviousness rejections are to be reviewed. Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, "a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaack*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1485 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). Contrary to the Examiner's position, the Applicants submit that Yguerabide does not teach or suggest what the Applicants have done.

The present invention is directed to nanoparticle-oligonucleotide probes comprising nanoparticles having oligonucleotides bound thereto, wherein each of the oligonucleotides has a covalently bound polythiol functional group that can bind to the nanoparticles. Previously, nanoparticle conjugates were prepared using conventional alkylthiol (RSH) or acyclic disulfide (RS-SR) and the resulting probes are quite sensitive to thiol cleaving reagents such as DTT which is present in many assay buffer solutions. The inventors have developed nanoparticle-oligonucleotides probes from oligonucleotides having covalently bound polythiol functional groups. The resulting probes have a surprising and unexpected enhanced stability towards such thiol cleaving reagents such as dithiothreitol (DTT). Example 25 (page 156 to 158 of the specification) includes a side-by-side comparison of three nanoparticle oligonucleotide probes prepared with oligonucleotides having covalently bound single thiols, cyclic disulfides, or a polythiol (e.g., trithiol). As discussed in this Example, DTT displaces the oligonucleotides from the probes, thereby enabling the gold nanoparticles to aggregate and exhibit a characteristic change in color from red to blue. The DTT displacement time was 1.5 hours (single thiol), 20

hours (cyclic disulfide) and 40 (polythiol) for these probes, demonstrating the unusual stability of nanoparticle-oligonucleotide probes prepared with oligonucleotides having covalently bound polythiol functional groups.

The Examiner alleged that the presently claimed invention is anticipated or obvious in that Yguerabide disclosed a detection method and gold particulate labels for the detection of analytes in a sample. With respect to a method of specific detection of one or more analytes in a sample, Yguerabide described a method of detection based on illumination and light scattering. See Yguerabide at col. 73 and 74. Col. 83 provides further discussion regarding particle size and particle binding to a surface. Cols. 77-80 relate to particles and their preparation. However, contrary to the Examiner's position, Yguerabide is completely silent with respect to any to nanoparticle conjugates having a covalently bound polythiol functional group and method for preparation of such conjugates.

The Examiner also alleged that Yguerabide taught detection and measurement of one or more analytes in a sample using gold particulate labeled probes and that the recited surface density is obvious. However, with respect to surface density, Yguerabide in col. 82, line 35, merely discusses surface density of the number of particles present in a spot on a substrate. Mere disclosure of particle density on a surface of a substrate is not a disclosure of oligonucleotide density on a surface of a particle. Col. 83 provides further discussion regarding particle size and particle binding to a surface. Cols. 77-80 relate to particles and their preparation. Col. 110 (Example 32) relates to a nucleic acid labeled particle but does not provide or suggest any particle surface density. Indeed, no particle surface density can be calculated from Yguerabide's disclosure since he does not provide any DNA concentrations that are necessary to calculate surface density. Thus, Yguerabide is completely silent with respect to any particle having oligonucleotides with the surface density recited in the present claims 433. Yguerabide cannot be relied on to support a section 102(e) or 103(a) rejection of the present claims.

Furthermore, the Examiner alleged that the recitations "recognition oligonucleotides" and "spacer portion" are overly broad and would encompass any nucleotide sequence. However, as described in the specification, "recognition oligonucleotides" refers to oligonucleotides which comprise a "sequence complementary to at least a portion of the sequence of a nucleic acid or oligonucleotide target." See page 79, lines 28-30. The "spacer portions" of the recognition

oligonucleotides allows for binding of the recognition oligonucleotides onto nanoparticles and for spacing away of the recognition portion of the recognition oligonucleotides away from the nanoparticle surface so that the recognition portion is more accessible for hybridization with a target. See page 80, lines 1-12. As discussed in the specification, the spacer portion may have any sequence which "does not interfere with the ability of the recognition oligonucleotides to become bound to the nanoparticles or to a nucleic acid or oligonucleotide target." See page 80, lines 12-17.

In light of the teachings in the specification, a person of ordinary skill in the art would appreciate that recognition oligonucleotides and spacer portions are not overly broad in their scope. Moreover, there is no discussion or suggestion anywhere in Yguerabide of any nanoparticle comprising recognition and spacer portions of recognition oligonucleotides as presently claimed.

In summary, the present claims recite limitations that are neither taught, made obvious, or suggested by the cited reference. Thus, the Applicant respectfully submits that Yguerabide cannot be applied to support section 102(e) and/or section 103(a) rejections of the claims. Withdrawal of these rejections is in order and is respectfully requested.

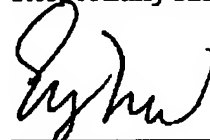
H. Conclusion

In light of the above amendment and discussion, the Applicants submit that the claims are in condition for an allowance. Notice to this effect is in order and is respectfully requested.

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. The Examiner is invited to contact the undersigned representative if the Examiner believes that this would be helpful in expediting the prosecution of this application.

Respectfully submitted,

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APPENDIX A

ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
00-1085-A	USSN 09/820,279 Filed 03/28/01	Mirkin, et al. / METHOD AND MATERIALS FOR ASSAYING BIOLOGICAL MATERIALS	Granted as US Pat. No. 6,750,016 Issued 06/15/04
00-1085-G	USSN 10/640,618 Filed 08/13/03	See 00-1085-A	Allowed
00-1086-A	USSN 09/903,461 Filed 07/11/01	Letsinger, et al. / METHOD OF DETECTION BY ENHANCEMENT OF SILVER STAINING	Granted as US Pat. No. 6,602,669 Issued 8/5/03
00-1124-A	USSN 09/998,936 Filed 11/30/01	Mirkin, et al. / SILVER STAINING REMOVAL BY CHEMICAL ETCHING AND SONICATION	Granted as US Pat. No. 6,726,847 Issued 04/27/04
00-1272-C	USSN 10/008,978 Filed 12/7/01	Mirkin, et al. / NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFOR	Granted as US Pat. No. 6,984,491 Issued 01/10/06
00-1272-F	USSN 11/050,983 Filed 02/04/05	See 00-1272-C	Pending
00-653-G	USSN 10/794,741 Filed 03/05/04	Mirkin, et al. / NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFOR	Pending
00-713-B1	USSN 09/923,625 Filed 08/07/01	Mirkin, et al. / NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFOR	Granted as US Pat. No. 6,773,884 Issued 08/10/04
00-713-C	USSN 09/344,667 Filed 06/25/99	See 00-713-B1	Granted as US Pat. No. 6,361,944 Issued 03/26/02
00-713-I	USSN 09/603,830 Filed 06/26/00	See 00-713-B1	Granted as US Pat. No. 6,506,564 Issued 01/14/03
00-713-I-1	USSN 09/961,949 Filed 09/20/01	See 00-713-B1	Granted as US Pat. No. 6,582,921 Issued 06/24/03
00-713-I-10	USSN 09/973,788 Filed 10/10/01	See 00-713-I-1	Granted as US Pat. No. 6,720,411 Issued 04/13/04
00-713-I-11	USSN 09/975,062 Filed 10/11/01	See 00-713-I-1	Granted as US Pat. No. 6,677,122 Issued 01/13/04
00-713-I-13	USSN 09/975,384	See 00-713-I-1	U.S. Patent No.

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	Filed 10/11/01		7,098,320
00-713-I-14	USSN 09/975,498 Filed 10/11/01	See 00-713-I-1	Granted as US Pat. No. 6,861,221 Issued 03/01/05
00-713-I-15	USSN 09/975,059 Filed 11/11/01	See 00-713-I-1	Granted as US Pat. No. 6,828,432 Issued 12/07/04
00-713-I-16	USSN 09/976,601 Filed 10/12/01	See 00-713-I-1	Granted as US Pat. No. 6,903,207 Issued 07/07/05
00-713-I-17	USSN 09/976,968 Filed 10/12/01	See 00-713-I-1	Granted as US Pat. No. 6,818,753 Issued 11/16/04
00-713-I-18	USSN 09/976,971 Filed 10/12/01	See 00-713-I-1	Granted as US Pat. No. 6,682,895 Issued 01/27/04
00-713-I-19	USSN 09/976,863 Filed 10/12/01	See 00-713-I-1	Granted as US Pat. No. 6,986,989 Issued 01/17/06
00-713-I-2	USSN 09/957,318 Filed 09/20/01	See 00-713-I-1	Granted as US Pat. No. 6,759,199 Issued 07/06/04
00-713-I-20	USSN 09/976,577 Filed 10/12/01	See 00-713-I-1	Granted as US Pat. No. 6,720,147 Issued 04/13/04
00-713-I-21	USSN 09/976,618 Filed 10/12/01	See 00-713-I-1	Granted as US Pat. No. 6,812,334 Issued 11/02/04
00-713-I-22	USSN 09/981,344 Filed 10/15/01	See 00-713-I-1	Granted as US Pat. No. 6,777,186 Issued 08/17/04
00-713-I-23	USSN 09/976,900 Filed 10/12/01	See 00-713-I-1	Granted as US Pat. No. 6,902,895 Issued 06/07/05
00-713-I-24	USSN 09/976,617 Filed 10/12/01	See 00-713-I-1	Granted as US Pat. No. 6,730,269 Issued 05/04/04
00-713-I-25	USSN 09/976,378 Filed 10/12/01	See 00-713-I-1	Granted as US Pat. No. 6,969,761 Issued 11/29/05
00-713-I-26	USSN 10/410,324 Filed 04/10/03	See 00-713-I-1	Granted as US Pat. No. 6,962,786 Issued 11/08/05
00-713-I-3	USSN 09/957,313	See 00-713-I-1	Granted as US Pat.

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	Filed 09/20/01		No. 6,645,721 Issued 11/11/03
00-713-I-4	USSN 09/966,491 Filed 09/28/01	See 00-713-I-1	Granted as US Pat. No. 6,610,491 Issued 08/26/03
00-713-I-5	USSN 09/966,312 Filed 09/28/01	See 00-713-I-1	Granted as US Pat. No. 6,673,548 Issued 01/06/04
00-713-I-6	USSN 09/967,409 Filed 09/28/01	See 00-713-I-1	Granted as US Pat. No. 6,740,491 Issued 05/24/04
00-713-I-7	USSN 09/974,500 Filed 10/10/01	See 00-713-I-1	Granted as US Pat. No. 6,709,825 Issued 03/23/04
00-713-I-8	USSN 09/974,007 Filed 10/10/01	See 00-713-I-1	Allowed
00-713-I-9	USSN 09/973,638 Filed 10/10/01	See 00-713-I-1	Granted as US Pat. No. 6,878,814 Issued 04/12/05
00-713-L	USSN 09/693,005 Filed 10/20/00	See 00-713-B1	Granted as US Pat. No. 6,495,324 Issued 12/17/02
00-713-M	USSN 09/693,352 Filed 10/20/00	See 00-713-B1	Granted as US Pat. No. 6,417,340 Issued 07/09/02
00-714-G	USSN 09/830,620 Filed 8/15/01	Mirkin, et al. / NANOPARTICLES WITH POLYMER SHELLS	Allowed
00-715-A	USSN 09/760,500 Filed 01/12/01	Mirkin, et al. / NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFOR	Granted as US Pat. No. 6,767,702 Issued 07/27/04
00-715-B	USSN 10/716,829 Filed 11/18/03	See 00-715-A	Pending
01-1565-A	USSN 10/266,983 Filed 10/08/02	Park, et al. / NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO AND USES THEREFOR	Allowed
01-1633-A	USSN 10/612,422 Filed 07/02/03	Storhoff, et al. / NANOPARTICLE POLYANION CONJUGATES AND METHOD OF USE THEREOF IN DETECTING ANALYTES	Pending
01-1705-A	USSN 10/108,211 Filed 03/27/02	Mirkin, et al. / BIO-BARCODES BASED ON OLIGONUCLEOTIDE- MODIFIED NANOPARTICLES	Granted as US Pat. No. 6,974,669 Issued 12/13/05

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ATTY Case No.	Serial No/ Filing Date	Inventors/Title	Status
01-1705-F	USSN 11/217,106 Filed 08/31/05	See 01-1705-A	Pending
01-565-A	USSN 10/125,194 Filed 04/18/02	Mirkin, et al. / DNA-BLOCK COPOLYMER CONJUGATES	Pending
01-599-A	USSN 10/291,291 Filed 11/08/02	Garimella, et al. / BIOCONJUGATE- NANOPARTICLE PROBES	Pending
01-661-A	USSN 10/034,451 Filed 12/28/01	Mirkin, et al. / DNA-MODIFIED CORE-SHELL AG/AU NANOCRYSTALS	Allowed
01-661-C	USSN 10/153,483 Filed 05/22/02	See 01-661-A	Allowed
01-661-E	USSN 10/397,579 Filed 3/26/03	See 01-661-A	Allowed
01-801-A	USSN 10/210,959 Filed 08/02/02	Cork, et al. / NANOPARTICLE IMAGING SYSTEM	Pending
01-897-B	10/194,138 Filed 07/12/02	Garimella, et al. / METHOD FOR IMMOBILIZING MOLECULES ONTO SURFACES	Pending
02-035-C	USSN 10/352,714 Filed 01/27/03	Patno, et al. / HYBRIDIZATION DEVICE AND METHOD	Pending
02-1227-A	USSN 10/735,357 Filed 12/12/03	Bao, et al. / DIRECT SNP DETECTION WITH UNAMPLIFIED DNA	Pending
02-307-A	USSN 10/437,753 Filed 05/14/03	Patno, et al. / MICROFABRICATED ELECTRODE ARRAY CHIP FOR ELECTRICAL DETECTION OF DNA HYBRIDIZATION	Pending
02-334-A	USSN 10/447,073 Filed 05/28/03	Garimella, et al. / METHOD FOR PREPARING SUBSTRATES HAVING IMMOBILIZED MOLECULES AND SUBSTRATES	Pending
02-334-B	USSN 11/124,609 Filed 05/06/05	See 02-334-A	Pending
02-338-B	USSN 10/172,428 Filed 06/14/02	Mirkin, et al. / MULTICHANNEL DETECTION USING NANOPARTICLE PROBES WITH RAMAN SPECTROSCOPIC FINGERPRINTS	Pending
02-338-C	USSN 10/431,341 Filed 05/07/03	See 02-338-B	Pending
03-214-A	USSN 10/789,831 Filed 02/27/04	Bao, et al. / LABEL-FREE GENE EXPRESSION PROFILING WITH UNIVERSAL NANOPARTICLE PROBES IN MICROARRAY ASSAY	Pending

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ATTY Case No.	Serial No./ Filing Date	Inventors/Title	Status
		FORMAT	
03-466-C	USSN 10/854,848 Filed 05/27/04	Storhoff, et al. / METHOD FOR DETECTING ANALYTES BASED ON EVANESCENT ILLUMINATION AND SCATTER- BASED DETECTION OF NANOPARTICLE PROBE COMPLEXES	Pending
03-466-E	USSN 10/995,051 Filed 11/22/04	See 03-466-C	Pending
03-666-E	USSN 10/877,750 Filed 06/25/04	Mirkin, et al. / BIO-BARCODE BASED DETECTION OF TARGET ANALYTES	Pending
03-666-G	USSN 11/127,808 Filed 05/12/05	See 03-666-E	Pending
04-060-A	USSN 11/121,165 Filed 05/03/05	Muller, et al. / APTAMER- NANOPARTICLE CONJUGATES AND METHOD OF USE FOR TARGET ANALYTE DETECTION	Pending
04-437-A	USSN 11/189,546 Filed 07/26/05	Ramakrishnan, et al. / METHOD FOR DISTINGUISHING METHICILLIN RESISTANT S. AUREUS FROM METHICILLIN SENSITIVE S. AUREUS IN A MIXED CULTURE	Pending